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Brief Research Communication

Schizophrenia and Chromosome 6p

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Several studies have recently reported genetic linkage between markers located on the short arm of chromosome 6 and schizophrenia. Valid conclusions, however, are difficult to formulate because chromosomal markers that yielded positive results span a relatively large region of chromosome 6, and studies did not necessarily obtain consistent results with regard to the particular loci tested. Here, we report a meta-analysis of the results of linkage studies of schizophrenia that used chromosome 6p markers. After conducting a systematic search, nine different studies were selected for the analysis using defined criteria. Pooled *P* values were obtained for all common markers investigated and provided additional support for a major susceptibility locus for schizophrenia in this region. In addition, two markers located 2 cM apart, D6S274 and D6S285, provided the most significant results. These findings may help narrow the chromosomal region in the search for a major gene implicated in schizophrenia. Am. J. Med. Genet. 74:195–198, 1997.

KEY WORDS: psychiatric disorder; linkage analysis; meta-analysis

INTRODUCTION

Schizophrenia is a chronic psychiatric disorder affecting up to 1% of the population. Although its etiology remains unknown, the involvement of genetic factors has been consistently demonstrated by family, twin, and adoption studies. However, the mode of inheritance remains uncertain, and particular loci involved in the transmission of this disorder are not yet well characterized [Kendler and Diehl, 1993]. Several articles have been published recently reporting linkage studies in schizophrenia with markers located in the short arm of chromosome 6. Although independent positive findings were found by different groups, fulfilling a basic requisite to confirm linkage [Lander and Kruglyak, 1995], there remains some controversy because the tested chromosomal markers span a considerably large region of chromosome 6 and studies were not necessarily coincident with respect to which chromosomal markers yielded positive results. One method for further investigation of the involvement of this chromosomal region in schizophrenia is by meta-analysis.

Quantitative synthesis, or meta-analysis, is an objective method to find, evaluate, and integrate past research that provides power and resolution by combining the results of independent statistical analysis [Mulrow, 1994]. An important advantage of standard meta-analytic procedures relies on allowing comparison of outcomes that were based on different scales or measured in different units [Rosenthal, 1984; Hedges and Olkin, 1985]. Although increasingly used in several areas of biomedical research, meta-analytic techniques have been scarcely employed in genetic studies. Recent articles, however, have suggested that meta-analysis would be a promising analytical tool to assist genetic analysis of complex traits [Lander and Kruglyak, 1995; Risch and Botstein, 1996]. One caution, however, in combining results of genetic mapping studies is that meta-analysis will be of limited application where genetic heterogeneity is such that there is no common genetic etiology within and between samples. Nevertheless, in circumstances of less extreme heterogeneity, meta-analysis can be useful to assess objectively, compare, and pool results such as lod scores or *P* values. Here, we report a meta-analysis of the linkage studies with chromosome 6p markers that aimed to identify which markers yielded consistent positive results, thereby helping to guide new investigations of this chromosomal region.

Methods to locate primary research articles were as follows. First, the National Library of Medicine Medline, Current Contents, PsycINFO, and BIOSIS databases were searched up to February 1996 using the key words "schizophrenia" and "chromosomes, human, pair

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6," or "chromosome 6". Second, the Medline database was searched by exploring related MeSH terms, namely, "schizophrenia," "schizoptypal personality disorder," "schizoid personality disorder," "chromosome mapping," "linkage (genetics)." Finally, the reference lists of review articles and primary studies were scanned to identify articles missed by the computerized search. In addition, recent publications not likely to have been already added to the databases were searched for relevant studies.

A total of 276 articles were identified; of these, only nine studies [Barr et al., 1994; Coon et al., 1994; Karayiorgou et al., 1994; Antonarakis et al., 1995; Moises et al., 1995; Mowry et al., 1995; Gurling et al., 1995; Schwab et al., 1995; Straub et al., 1995] were included in this meta-analysis (Table I). The following inclusion and exclusion criteria were used: (1) diagnoses made according to a standard diagnostic criteria, (2) use of a linkage study design (candidate loci and/or genome screens), and (3) test of chromosome 6 markers. Analysis of part or the same data set for identical chromosome markers reported in another publication (nonindependence between studies) and meeting abstracts (insufficient information reported) were excluded. Two articles presented results for identical markers in the same data set [Straub et al., 1995; Wang et al., 1995]. We included the study that analyzed a larger sample [Staub et al., 1995]. Three meeting abstracts were excluded [Riley et al., 1995; Wang et al., 1995; Wildenauer et al., 1995]. A single reviewer (G.T.) identified, selected, and assessed the studies. However, a reliability test with a second reviewer for inclusion and exclusion criteria showed excellent agreement ($\kappa = 1.0$).

Six variables were defined that were either identified through the text of the publications or calculated from the information reported. It was decided to categorize studies according to chromosomal markers and to use marker results as unifying factors for data pooling; in other words, we combined the studies by grouping results for each genetic marker investigated rather than using a certain group of results or a global estimate for each study. The number of outcomes per study to be included in a meta-analysis is an important issue because pooling nonindependent results may introduce important errors [Rosenthal, 1984; Hedges and Olkin, 1985].

In order to have an appropriate sample of independent estimators, we selected only one outcome per marker per study. The decision regarding which outcome to select was based on statistical significance: either maximum lod score maximized over the different genetic models tested [Hodge and Elston, 1994], or smallest P value (when only nonparametric methods were used), applying the same criterion to all studies. It is possible to compare and combine results from different studies only when the measurement they report is of the same nature. In this meta-analysis, combined outcomes were nominal P values; therefore, when the selected outcome was a lod score, a P value was estimated by a one degree of freedom Chi-square transformation (one-sided) [Ott, 1985]. Considering the number and characteristics of the studies to be pooled, the weighted inverse normal method of assessing significance of combined results across studies was chosen [Rosenthal, 1984; Hedges and Olkin, 1985], where the weight was the number of families. This modification of the Stouffer method is based on combining weighted standard normal deviates (Z-score) associated with each P value and adjusting for the number of studies being included. In addition, before the pooling of data, a test of statistical homogeneity was carried out in order to assess differences among Z scores [Rosenthal, 1984]. According to the outcome of this test, among 19 markers commonly investigated (by at least 2 independent studies), results for 11 markers could be combined (Table II).

The meta-analysis of linkage results for most of the pooled markers provides further support for the hypothesis that there is at least one locus predisposing to schizophrenia on the short arm of chromosome 6. The obtained P values correspond to an overall estimate of the probability of observing the data for the null hypothesis of no linkage between schizophrenia and markers of this region of chromosome 6. They also serve as indicators of aberrations present among studies, and as such they are useful in determining result consistency [Olkin, 1995]. Therefore, these results are robust considering that the studies included in this meta-analysis investigated families of various ethnic origins and employed different genetic models and phenotypic classifications. Because the criterion for combining the results of the independent studies was based on homogeneity analysis, the markers for which results could be pooled reflect common tendencies of linkage among stuides. Markers D6S274 and D6S285, located ~2 cM apart, showed the most significant results ($P = 0.00003$ and $P = 0.00008$, respectively). This finding may help guide further investigations searching for a major susceptibility gene for schizophrenia on chromosome 6p.

Although the ideal meta-analytic approach would be to undertake a linkage analysis of the raw data from studies, this is frequently impractical since these data are usually unavailable in publications. In addition, methodological differences between studies must be carefully considered before attempting such procedure. In fact, it is precisely this kind of scenario that stimulated the development of meta-analytic techniques [Hedges and Olkin, 1985]. Another important issue to be considered refers to certain methodological limitations of meta-analysis, particularly the effect of unpublished negative reports (the file-drawer problem), which is a well-known bias [Rosenthal, 1984]. However, it is likely that a linkage study investigating chromosome 6p markers in schizophrenia would be published regardless of whether their results were negative or positive in view of the current importance of the subject. Finally, although it would have been useful to investigate covariates, specific clusters, or trends among the pooled studies, this was impractical because of limited data. Further meta-analysis, including future studies investigating linkage of schizophrenia with the same chromosome 6p markers, will help elucidate demographic, diagnostic, and modeling issues that may play important roles in obtaining evidence for linkage. Indeed, methods for cumulative meta-analysis are

TABLE I. Characteristics of Identified Studies

Study	Year	Families	Population[a]	Diagnostic criteria	Instruments	Loci
Barr et al.	1994	1	Swedish	Feighner DSM-III	SADS-L	D6S19, D6S20, D6S23, D6S26, D6S27, D6S87, DQA, PLG
Coon et al.	1994	9	West European Spanish	RDC	SADS	CNR, D6S4, D6S8, D6S10, D6S21, D6S29, D6S30, D6S37, D6S44, D6S87, D6S129, D6F14S1, F13A1, MYB, SOD2, TCP10
Karayiorgou et al.	1994	39	American	DSM-III-R	DIS + PSE	D6S89, D6S268, D6S275, D6S276, D6S292, D6S295, DHFRP2
Antonarakis et al.	1995	57	American	DSM-III-R	DIS SID-P FH-RDC	D6S259, D6S260, D6S277, D6S285, D6S296, D6S477, D6S1011
Moises et al.	1995	5/65	Australian American Canadian Chinese German Italian Scottish Swedish	RDC or DSM-III-R	SADS-L	D6S257, D6S259, D6S260, D6S261, D6S262, D6S263, D6S264, D6S269, D6S271, D6S272, D6S273, D6S274, D6S275, D6S276, D6S279, D6S281, D6S285, D6S286, D6S290, D6S291, D6S292, D6S297, D6S299, D6S305, D6S306, D6S309, D6S344,
Mowry et al.	1995	45	Australian American	DSM-III-R	SADS CASH SSP/SIB SIDP	D6S259, D6S285, D6S296, D6S470
Gurling et al.	1995	23	British Icelandic	RDC	SADS-L	D6S285, D6S296
Schwab et al	1995	54	German Israeli	RDC	SADS-L	CAR, D6S258, D6S260, D6S265, D6S271, D6S273, D6S274, D6S276, D6S277, D6S282, D6S285, D6S288, D6S291, D6S296, D6S299, D6S309, D6S422, D6S429, D6S439, D6S443, D6S461, D6S464, D6S470, D6S89, F13A1
Straub et al.	1995	265	Irish	DSM-III-R	SCID SIS	D6S105, D6S259, D6S260, D6S273, D6S274, D6S276, D6S277, D6S285, D6S291, D6S296, D6S299, D6S422, D6S443, D6S470, D6S477, F13A1

[a] As described by the authors.

TABLE II. Z-scores With Nominal *P* Values for Combined Results for Chromosome 6p Loci*

Loci	Number of families	Z score	*P* value
D6S477	322	1.04	0.14920
D6S470	364	3.54	0.00020
D6S443	319	1.97	0.02440
D6S259	372	2.93	0.00170
D6S260	381	3.02	0.00130
D6S274	384	4.19	0.00003
D6S285	449	3.94	0.00008
D6S422	319	2.85	0.00220
D6S299	324	2.53	0.00570
D6S273	324	2.45	0.00710
D6S291	384	2.83	0.00230

* Listed in order from telomere to centromere direction.

available that allow for continuous incorporation of new studies [Mulrow, 1994]. Other combining methods, e.g., two-point linkage analysis using mapping functions [Schaid and Elston, 1994] also will be of utility should raw data be available.

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REFERENCES

Antonarakis SE, Blouin JL, Pulver AE, Wolyniec P, Lasseter VK, Nestadt G, Kasch L, Babb R, Kazazian HH, Dombroski B, Kimberland M, Ott J, Housman D, Karayiorgou M, MacLean CJ (1995): Schizophrenia susceptibility and chromsome 6p24-22. Nature Genet 11:235–236.

Barr CL, Kennedy JL, Pakstis AJ, Wetterberg L, Sjorgren B, Bierut L, Wadelius C, Wahlstrom J, Martinsson T, Giuffra L, Gelernter J, Hallmayer J, Moises HW, Kurth J, Cavalli-Sforza LL, Kidd KK (1994): Progress in a genome scan for linkage in schizophrenia in a large Swedish kindred. Neuropsych Genet 54:51–58.

Coon H, Jensen S, Holik J, Hoff M, Myles-Worsley M, Reimherr F, Wender P, Waldo M, Freedman R, Leppert M, Byerley W (1994): Genomic scan for genes predisposing to schizophrenia. Neuropsych Genet 54:59–71.

Gurling H, Kalsi G, Chen AHS, Green M, Butler R, Read T, Murphy P, Curtis D, Sharma T, Petursson H, Brynjolfsson J (1995): Schizophrenia susceptibility and chromsome 6p24-22. Nature Genet 11: 234–235.

Hedges LV, Olkin I (1985): "Statistical Methods for Meta-analysis." Orlando: Academic Press.

Hodge SE, Elston RC (1994): Lods, wrods, and Mods: The interpretation of lod scores calculated under different models. Genet Epidemiol 11:329–342.

Karayiorgou M, Kasch L, Lasseter V, Hwang J, Elango R, Bernardini DJ, Kimberland M, Babb R, Francomano CA, Wolyniec PS, Lamacz M, Nestadt G, Meyers D, Ott J, Childs B, Antonarakis S, Kazazian HH, Housman D, Pulver A (1994): Report from the Maryland epidemiology schizophrenia linkage study: No evidence for linkage between schizophrenia and a number of candidate and other genomic regions using a complex dominant model. Neuropsych Genet 54: 345–353.

Kendler KS, Diehl SR (1993): The genetics of schizophrenia: A current, genetic-epidemiologic perspective. Schizophr Bull 19:261–285.

Lander E, Kruglyak L (1995): Genetic dissection of complex traits: guidelines for interpretating and reporting linkage results. Nature Genet 11:241–247.

Moises HW, Yang L, Kristbjarnarson H, Wiese C, Byerley W, Macciardi F, Arolt V, Blackwood D, Liu X, Sjogren B, Aschauer HN, Hwu HG, Jang K, Livesley WJ, Kennedy JL, Zoega T, Ivarsson O, Bui MT, Yu MH, Havsteen B, Commenges D, Weissenbach J, Schwinger E, Gottesman II, Pakstis AJ, Wetterberg L, Kidd KK, Helgason T (1995): An international two-stage genome-wide search for schizophrenia susceptibility genes. Nature Genet 11:321–324.

Mowry BJ, Nancarrow DJ, Lennon DP, Sandkuijl LA, Crowe RR, Silverman JM, Mohs RC, Siever LJ, Endicott J, Sharpe L, Walters MK, Hayward, Levinson DF (1995): Schizophrenia susceptibility and chromsome 6p24-22. Nature Genet 11:233–234.

Mulrow C (1994): Rationale for systematic reviews. BMJ 309:597–9.

Ott J (1991): "Analysis of human genetic linkage," 2nd ed. Baltimore: Johns Hopkins University Press.

Olkin I (1995): Statistical and Theoretical considerations in meta-analysis. J Clin Epidemiol 48:133–146.

Riley BP, Mogudi-Carter M, Rajagopalan S, Jenkins T, Williamson R (1995): No evidence for linkage of schizophrenia to the short arm of chromosome 6 in a sample of southern African Bantu-speaking families. Am J Hum Genet 57:A201.

Risch N, Botstein D (1996): A manic depressive history. Nature Genet 12:351–353.

Rosenthal R (1984): "Meta-analytic Procedures for Social Research." Beverly Hills, CA.: Sage.

Schaid DJ, Elston RC (1994): Combining two-point genetic linkage analyses using mapping functions. Genet Epidemiol 11:1–17.

Schwab SG, Albus M, Hallmayer J, Honig S, Borrmann M, Lichtermann D, Ebstein RP, Ackenheil M, Lerer B, Risch N, Maier W, Wildenauer DB (1995): Evaluation of a susceptibility gene for schizophrenia on chromosome 6p by multipoint affected sib-pair linkage analysis. Nature Genet 11:325–327.

Straub RE, MacLean CJ, O'Neil A, Burke J, Murphy B, Duke F, Shinkwin R, Webb bT, Zhang J, Walsh D, Kendler KS (1995): A potential vulnerability locus for schizophrenia on chromosome 6p24-22: Evidence for genetic heterogeneity. Nature Genet 11:287–293.

Wang S, Detera-Wadleigh S, Coon H, Sun C, Goldin LR, Byerely WF, Gershon ES, Diehl SR (1995): Further evidence for a susceptibility locus for schizophrenia on chromosome 6p23. Am J Hum Genet 57:A36.

Wang S, Sun C, Walczak CA, Ziegele JS, Kipps BR, Goldin LR, Diehl SR (1995): Evidence for a susceptibility locus for schizophrenia on chromosome 6pter-p22. Nature Genet 10:41–46.

Wildenauer DB, Scwab SG, Eckstein G, Zill P, Honig S, Hallmayer J, Albus M, Bormann M, Ebstein RE, Lichtermann D, Lerer B, Risch N, Maier W (1995): Searching for susceptibility genes in schizophrenia by affected sib pair analysis: Evidence for loci in 22q, 5q, and 6p. Am J Hum Genet 57:A36.